

**IN THE UNITED STATES PATENT AND TRADEMARK OFFICE**

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In re Patent Application of:  
Gavril W. Pasternak

Application No.: 10/509,050

Confirmation No.: 2704

Filed: October 27, 2004

Art Unit: 4133

For: SYNERGISTIC L-METHADONE  
COMPOSITIONS AND METHODS OF USE  
THEREOF

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Examiner: J. L. Karol

**DECLARATION OF DR. CHARLES E. INTURRISI PURSUANT TO 37 C.F.R. §1.132**

Commissioner for Patents  
P.O. Box 1450  
Alexandria, VA 22313-1450

Dear Sir/Madam:

I, the undersigned, Dr. Charles E. Inturrisi, hereby declare as follows:

1. I am a Professor of Pharmacology at the Weill Cornell Medical College, a part of Cornell University, located in New York, NY. I have a Ph.D. in Pharmacology from the Tulane University and a B.S. in Pharmacy from The University of Connecticut.

2. My research activities are directed toward the development of methods for the alleviation of pain and drug addiction. My laboratory is investigating the role of glutamate receptors in the neuronal plasticity that is manifest as injury-induced pain as well as opioid tolerance, dependence and addictive behaviors. At the clinical level, my group discovered that the d isomer of methadone is a nonopioid, NMDA receptor antagonist in animal studies and we are planning to evaluate the safety and efficacy of this compound in patients with pain to discover new treatments for pain and drug addiction. I am the author of a number of scientific journal articles in this topic as well as the inventor of United States Patent No. 6,008,258.

3. I am familiar with the above-identified application for U.S. Patent (the “Application”) and with rejected Claims 3-9 and 20-25 thereof. I understand that, in an Office Action issued from the U.S. Patent Office on October 15, 2009, the Examiner has rejected Claims 3-9 and 20-25 as allegedly obvious in view of Dahlstrom et al. (“Relation Between Morphine Pharmacokinetics and Analgesia,” *Journal of Pharmacokinetics and Biopharmaceutics*, Vol. 6, No. 1, 1978, Pgs. 41-53) (“Dahlstrom”) in view of United States Patent No. 6,008,258 to Inturissi (“the ‘258 Patent”).

4. I understand that the Examiner contends that Dahlstrom teaches the administration of morphine to elicit an analgesic effect and that the ‘258 Patent teaches that D-methadone is a 50-fold less potent analgesic in humans than L-methadone.

5. I understand that that Examiner contends that the ‘258 Patent teaches that the L isomer is active for analgesia.

6. I also understand that the Examiner contends that one of ordinary skill in the art would have been motivated to combine morphine and L-methadone, or an increased amount of L-methadone, because combining individual compounds taught to have the same utility (in this case analgesia) to form a new composition for the same purpose is obvious.

7. In my opinion, with regard to analgesia, this is incorrect.

8. At the time of the Application, one of ordinary skill in the art would not have been motivated to use a combination of two opioid analgesic agents to effect analgesia.

9. Prior to the Application, it was believed that use of two opioid analgesic agents would have had little added benefit as the two agents would compete for the same receptors and would thus be no more effective than using one agent at full dosage. If a second agent were to be used, one of ordinary skill in the art at the time would have utilized an analgesic agent which acted on a different set of receptors.

10. Indeed, my colleagues and I would teach our pharmacology students that in order to optimize the management of pain they should utilize *a single opioid at a time* either alone or in combination with a non-opioid drug.

11. As such, I do not believe that one of ordinary skill in the art, upon reading the disclosure of the '258 Patent, would have been motivated to combine L-methadone with a second opioid analgesic. At best, one of ordinary skill in the art may have been motivated to utilize L-methadone *alone* for its analgesic properties.

12. I hereby further declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true, and further that these statements are made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment or both (18 U.S.C. 1001), and that such willful false statements may jeopardize the validity of the above-identified Application or any patent issued thereon.

Date: \_\_\_\_\_

CHARLES E. INTURRISI

Digitally signed by CHARLES E. INTURRISI  
DN: cn=CHARLES E. INTURRISI, o=US, ou=WEILL CORNELL MEDICAL  
COLLEGE, ou=PHARMACOLOGY, email=cintur@med.cornell.edu  
Reason: I am the author of this document  
Date: 2010.01.13 09:12:46 -05'00'

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Dr. Charles E. Inturrisi